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Suppressive Effect of Iodine on DMBA-Induced Breast Tumor Growth in the Rat

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Concerning the suppressive effect of inorganic iodine on the growth of 7,12-dimethyl-benz(a)anthracene (DMBA)-induced breast tumor in female Sprague-Dawley (SD) rats, we previously reported that although iodine itself had a suppressive effect on the tumor growth, its effect was not as strong as that of MPA (medroxy-progesterone acetate). However, the combined medication of iodine at a low concentration + MPA showed a stronger effect than MPA alone. The purpose of the present study is to elucidate this mechanism of action by determining the uptake of the administered iodine into breast tumor tissue. Breast tumors were induced with DMBA in female SD rats, and these animals were treated with MPA + inorganic iodine at various concentrations for 4 weeks to determine tumor growth and tumor iodine content. In the comparison of tissue iodine content in growth-suppressive tumors with that in nonsuppressive tumors, the former showed a much higher iodine content. This suggests that direct uptake of inorganic iodine by breast tumors led to the suppression of tumor growth.

KEY WORDS: 7,12-dimethyl benz(a)anthracene (DMBA), rat, iodine, tissue iodine content

INTRODUCTION

A considerable amount of research has been reported on the relationship between breast cancer and thyroid disease [1–4]. Some of this research indicates that breast cancer frequently occurs in hypothyroid patients, whereas some considers hyperthyroid patients at higher risk of developing breast cancer. 131I has been used as an antihyperthyroid therapy, and several reports have pointed out the breast cancerogenic risk of this radioactive iodine therapy [3,4]. Recently, several authors have reported no relationship between thyroid disease and breast cancer [5,6]. A study has indicated that many Japanese women with breast cancer show decreased free T3 and free T4 levels [7]. The relationship between these two diseases has thus attracted great attention. However, there are also many reports on the correlation between iodine intake and thyroid disease [8,9].

Noting all reports, we focused on the possible relationship between iodine and breast cancer and conducted an experiment administering iodine preparation to Sprague-Dawley (SD) rats bearing 7,12-dimethyl benz(a)anthracene (DMBA)-induced breast tumor. As a result, iodine alone had a suppressive effect on the tumor growth compared with the control group. However, the combination of iodine at a low concentration and medroxy-progesterone acetate (MPA) remarkably suppressed the growth of breast tumor [10]. In the present study, with the aim of elucidating this mechanism of action, we determined the

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TABLE I. Five Groups of Rats Treated by Various Medications

Groups	Number of rats	Medications[a]	
Control	15	saline	
MPA	15	MPA	6.0 mg/body/day
MPA + I − A	15	MPA	6.0 mg/body/day
		I_2	0.25 mg/body/day
MPA + I − B	15	MPA	6.0 mg/body/day
		I_2	0.025 mg/body/day
MPA + I − C	15	MPA	6.0 mg/body/day
		I_2	0.0025 mg/body/day

[a] MPA: medroxyprogesterone acetate; I_2: inorganic iodine.

changes of tumor iodine content after administration of the iodine preparation and MPA.

MATERIALS AND METHODS

At 60 days of age, female SD rats received 20 mg of DMBA dissolved in sesame oil by gastric intubation. About 10–11 weeks following the administration, breast tumors developed in ~80% of rats. These rats were randomly divided into five different medication groups (Table I). Five rats in each group were sacrificed before medication, at the end of the medication period of 4 weeks, and 4 weeks after its discontinuation, and tissue iodine content was determined in each initially developing tumor. In each rat, the tumor size (major and minor axes) was measured every week to investigate the suppressive effect of each medication on the tumor growth. As shown in Table I, the rats were allotted to different medication groups receiving physiological saline, MPA alone, or MPA + diluted Lugol's solution at three different concentrations. Lugol's solution contains 1 g of iodine and 2 g of potassium iodide in 100 ml of water. As clinically 1,200 mg/body of MPA was used for human breast cancer, 6 mg/body of MPA was administered after calculation of 1,200 mg/body of human (standard Japanese female weight; 50 kg) in terms of rat weight (250 g). Each of these doses was given for 4 weeks, and observation was continued for 4 weeks after administration ended (Table I).

To determine total iodine content in tissue, 0.2 g of breast tumor tissue was heated after the addition of KOH and carbonated in an electric furnace. It was dissolved

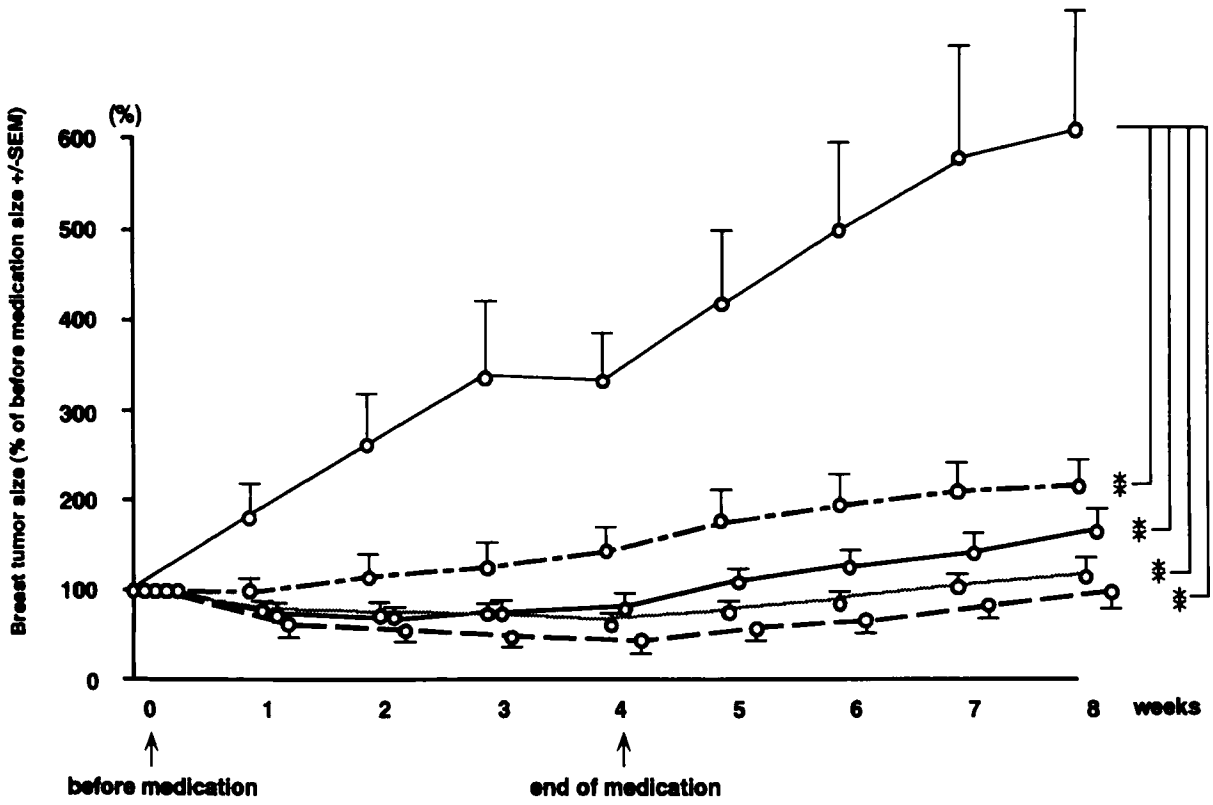

Fig. 1. Changes of breast tumor size during 8 experimental weeks were compared in five groups. Tumor growth was significantly suppressed in MPA + iodine groups in comparison with control group ($P < 0.01$). Tumor size at each point was shown by percent change compared with size at premedication point. Standard error of the mean was indicated. Numbers of rats in each group at the three points of before medication, end of medication, and 4 weeks after end of medication were 15, 10, and 5. (MPA, medroxy-progesterone acetate; Control, ——; MPA, ▬; MPA + I-A, — - —; MPA + I-B, —— ; MPA + I-C, — — —.)

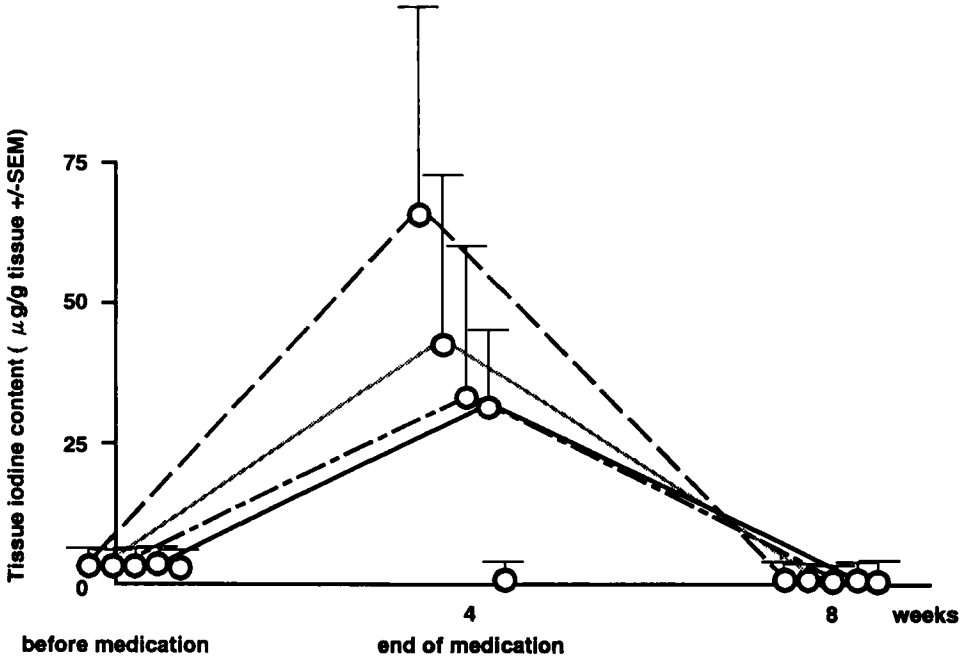

Fig. 2. Five rats were sacrificed in each group at the three points and tissue iodine content in breast tumor was measured. Highest iodine content was noticed in MPA + I-C group at the end of medication. Every group showed very low tissue iodine content before medications and at 8 experimental weeks. Each group showed not-significant changes at 0, 4, and 8 experimental weeks. (MPA, medroxy-progesterone acetate; Control, ——; MPA, ▬▬; MPA + I-A, —— · ——; MPA + I-B, ▬ · ▬ ; MPA + I-C, —— · · ——.)

in distilled water, centrifuged to obtain the supernatant, and colorimetric analysis was carried out with arsenious acid and cerium [11,12].

At 4 weeks after stopping medication, hormone-related organs, thyroid, adrenal glands, and ovaries were removed from each rat, and the respective tissue iodine contents were measured.

One-way analysis of variance (NOVA) method was used for the statistical evaluation for data.

RESULTS

Changes of Tumor Size in Each Medication Group

Changes in tumor size were compared among the five medication groups, including the control group. As in the earlier reported experiment [10], the combination of MPA and iodine significantly suppressed the tumor growth in comparison with the control group in the present study. This tendency was most remarkable in the group treated by the combination of MPA and iodine at the lowest concentration (Fig. 1).

Changes of Tumor Iodine Content in Each Medication Group

Figure 2 shows the changes of total iodine content in tumor at the three points of measurement. At the end of medication, the groups receiving iodine in combination with MPA had higher tumor iodine content in inverse proportion to the concentration of the administered iodine preparation. It remains unclear, however, why a considerable amount of iodine was detected in tumors of the animals treated with MPA alone. In all but the controls, as high as ~30 μg of iodine per g of tissue was detected even in the group showing the lowest tumor iodine content. At 4 weeks after administration ended, virtually no iodine was detected in tumors. However, the difference of iodine content in each group at the three points of measurement was not significant by statistical evaluation using the one-way NOVA method.

Although commercially available normal diet for rats contains a very small amount of iodine, the tumor iodine content before medication in every group was very low at 2.90 ± 0.98 μg/g tissue. This suggested that the iodine detected after medication did not derive from food itself (Fig. 2).

Comparison of Iodine Contents Between Effective and Noneffective Cases

Tumors that were remarkably shrunk in size (n = 6) and those showing continuous growth (n = 6) at the end of the 4-week medication period were selected at random, and tumor iodine content was determined. All the six suppressed tumors showed high iodine content with the mean value of 106.3 ± 1.96 μg/g tissue. In the nonsuppressed tumors, however, the mean iodine content was as low as 1.125 ± 1.96 μg/g tissue.

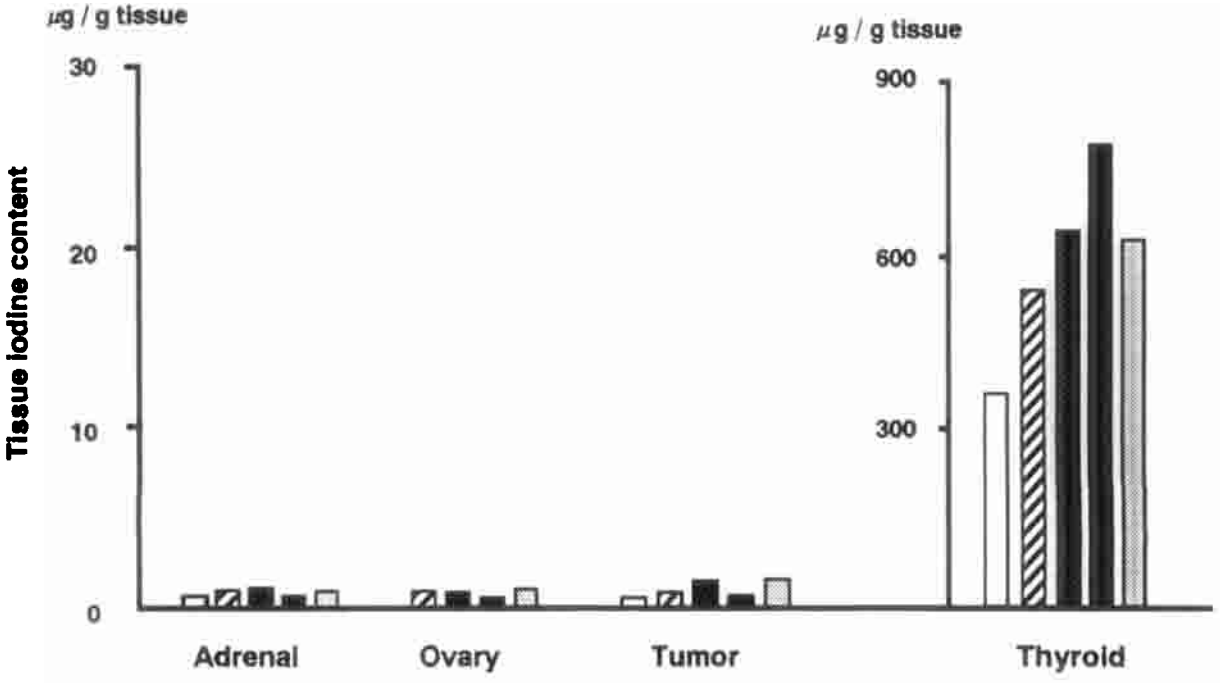

Fig. 3. At 8 experimental weeks, tissue iodine contents in various hormone-related organs were measured. Remarkably high levels of iodine content were found in thyroid gland at weeks after end of medication. (MPA, medroxy-progesterone acetate; Control, □; MPA, ▨; MPA + I-A, ■; MPA + I-B, ■; MPA + I-C, ▩.)

Tissue Iodine Content in Main Hormone-Related Organs at 4 Weeks After Stopping Medication

At the end of the experiment, the adrenal glands, ovaries, thyroid gland, and breast tumors were removed in each group, and tissue iodine content was determined. In all treated groups, almost no iodine was detected in the former two organs, but the thyroid gland contained about a 1,000-fold higher concentration of iodine. This tendency did not differ with the medication (Fig. 3).

DISCUSSION

Although all the tumors showing growth contained almost no iodine, a large amount of iodine was detected in the shrunken tumors. Thus the tumor growth was highly suppressed with a large iodine uptake, and there was no suppression if there was no uptake. From the fact that the tumor growth was suppressed by much tumor uptake of inorganic iodine, we think that iodine itself exerted a certain direct effect on tumor tissues.

Iodine administered at a lower concentration had a rather stronger suppressive effect on tumor growth and was transferred into the tumor at a higher level (Fig. 1,2). This seemingly contradictory phenomenon suggests that simultaneously administered MPA might play some role in the tumor iodine uptake.

As shown in Figure 3, much of the administered iodine was taken up by the thyroid gland and remained in large quantity after medication was stopped. We therefore suppose that a small amount of iodine is sufficient to be transferred into the tumor and thereby suppress its growth.

Bernard has published a similar report [13], in which he revealed that administered iodine is taken up by not only the thyroid gland but also by the stomach or mammary gland and that deficient iodine intake causes a change in the mammary gland tissue as well as the thyroid gland. Furthermore, he found that when DMBA was administered to hypothyroid or iodine-deficient rats, breast tumors developed earlier than in normal rats. His report supports our finding that iodine might directly suppress the growth of rat breast tumor.

We intend to pursue this line of study by establishing a clinically applicable experimental system.

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